

REMARKS

Claims 52-56, 58-63, 66, and 68-71 were pending prior to this Response. Applicants cancel Claims 53-55 and 62, amend Claims 52, 63, 66, 68-71, and add new Claims 72-73. Claims 52, 56, 58-61, 63, 66 and 68-73 will be pending after this Response.

Support for the Amendments and the New Claims

The amendments and the new claims do not add any new matter and are supported throughout the application, as filed. Claim 52 is amended to incorporate the limitations of Claim 55, cancelled as redundant. The support for the amendments is also found, for example, on page 8, line 34, through page 9, line 3, and on page 10, lines 8-11, of the specification. Claim 63 is amended to incorporate the limitations of Claims 53-55. The support for the amendments is also found, for example, on page 13, lines 11-15 of the specification. Support for new Claims 72-73 is found, for example, on page 10, lines 20-21 and 31-32, of the specification. Applicants also amend the claims for clarity and consistency.

Rejections under 35 U.S.C. §103(a)

MPEP 2142 states: “To reach a proper determination under 35 U.S.C. §103, the examiner must step backward in time and into the shoes worn by the hypothetical ‘person of ordinary skill in the art’ when the invention was unknown and just before it was made. In view of all the factual information, the examiner must then make a determination whether the claimed invention ‘as a whole’ would have been obvious at that time to that person.” To reject a claim as obvious, the Examiner, first, must resolve the *Graham* factual inquiries, namely, (a) determining the scope and content of the prior art, (b) ascertaining the differences between the claimed invention and the prior art, and (c) resolving the level of ordinary skill in the pertinent art. *See* MPEP 2141(II) citing *Graham v. John Deere Co.*, 383 U.S. 1 (1966).

Eyles (Vaccine Vol. 16(7):698-707 (1998); “Eyles”) in view of Amsden et al. (WO 99/57176; “Amsden”) and further in view of Duncan et al. (WO 94/20070; “Duncan”)

The Examiner rejects Claims 52, 55-56, 58-63, 66 and 68-71 under 35 U.S.C. §103(a) as obvious over *Eyles* in view of *Amsden* and further in view of *Duncan*. Applicants cancel Claims 55 and 62, thereby rendering their rejection moot. Applicants assert that the amendments

to independent Claims 52 and 63 overcome the rejection of Claims 52, 56, 58-61, 63, 66 and 68-71. Independent Claim 52, as currently amended, recites a pharmaceutical composition comprising a biologically active agent capable of generating a protective immune response in an animal or a human and an immunostimulant amount of N-carboxymethyl chitosan or a salt thereof, wherein the biologically active agent and the immunostimulant amount of N-carboxymethyl chitosan or the salt thereof are encapsulated in microspheres or microparticles comprising a polymeric material of a molecular weight 94 kDa or more. Independent Claim 63, as currently amended, recites a pharmaceutical composition comprising a polymeric microparticle surface modified or coated with N-carboxymethyl chitosan or a salt thereof and an adsorbed onto the microparticle biologically active agent capable of generating a protective immune response in an animal or a human. Generally, independent Claims 52 and 63 are directed to embodiments of the compositions invented by applicants, in which an immunostimulant agent, N-carboxymethyl chitosan, is associated with a microparticle comprising an immunogenic biologically active agent.

Applicants assert that the combination of the publications cited by the Examiner fails to render obvious the claimed embodiments at least in view of the differences between the claims and the scope and content of the cited publications. Applicants discussed the scope and content of Eyles, Amsden and Duncan in the Amendment and Response to Final Office Action filed February 13, 2009, and in the Amendment and Response to Non-Final Office Action filed August 31, 2009 (“previous Responses”). Applicants bring to the Examiner’s attention that the cited publications, taken separately or in combination, fail to disclose or suggest claimed embodiments of applicants’ compositions.

Eyles discloses and compares immunogenic properties of two distinct compositions comprising microencapsulated antigens. *See*, for example, Eyles, page 705, Table 1. The first composition, listed in the first row of Table 1 in Eyles, comprises microencapsulated antigens. The second composition, listed in the third of Table 1 in Eyles, comprises a combination of co-encapsulated antigens and adjuvant CTB (cholera toxin). Eyles fails to disclose or suggest using N-carboxymethyl chitosan in the microencapsulated compositions, as recited in the currently pending claims. Eyles also fails to disclose or suggest associating the adjuvant (CTB) or any other immunostimulant with the microcapsules containing the antigen in order to improve

immunogenicity of the microencapsulated antigen. In particular, Eyles fails to disclose or suggest microencapsulated compositions comprising microparticles in which a biologically active agent is co-encapsulated with an immunostimulant agent (as recited in Claim 52) or microparticles surface-modified with an immunostimulant agent and having adsorbed a biologically active agent (as recited in Claim 63).

Amsden fails to add any knowledge to the disclosure of Eyles that would help one of ordinary skill in the art to arrive at the claims, as currently amended. Amsden discloses a method for forming microspheres and discloses microsphere compositions for the delivery of bioactive drugs, including antigens. *See* Amsden, Abstract and pages 23-24. Amsden lists polysaccharides, including N-carboxymethyl chitosan, as polymers capable of forming microspheres. *See* Amsden, page 9. The Examiner asserts on pages 5-6 and 8 of the Office Action that Amsden disclosed the compositions recited in the rejected claims (pending prior to the present Response) but for the cationic pluronic element of the claims.

Applicants disagree with the Examiner's interpretation of Amsden. Applicants assert that Amsden does not disclose polymer microspheres comprising N-carboxymethyl chitosan as a separate component in addition to the microencapsulating polymer, as claims pending prior to the present response recited, and as the currently amended claims continue to recite. Accordingly, applicants assert that it would not have been obvious to one of ordinary skill in the art using the combined disclosure of Eyles and Amsden to arrive at compositions in which N-carboxymethyl chitosan is co-encapsulated with a biologically active agent, as recited in Claim 52, or at compositions comprising polymer microspheres surface-modified with N-carboxymethyl chitosan, as recited in Claim 63.

Applicants assert that, based on the disclosure of Amsden, one of ordinary skill in the art would not have found it obvious to add N-carboxymethyl chitosan to the microspheres recited in Eyles in order to arrive at the composition recited in the claims. Applicants bring to the Examiner's attention that MPEP 2143.01(IV) requires "some articulated reasoning with some relational underpinning to support the legal conclusion of obviousness" (internal citations omitted). Applicants assert that, in the Office Action, the Examiner failed to provide articulate reasoning why of ordinary skill in the art would have added N-carboxymethyl chitosan,

identified in Amsden as one of many possible polymers for the formation of microparticles, to the microencapsulated compositions already disclosed in Eyles. Accordingly, the Examiner failed to establish *prima facie* obviousness of the rejected claims for at least this reason.

Applicants bring to the Examiner's attention Eyles and Amsden, taken separately or in combination, fail to disclose or suggest using N-carboxymethyl chitosan as an immunostimulant agent, whereas Claim 52, as currently amended, recites an immunostimulant amount of N-carboxymethyl chitosan. Applicants also respectfully bring to the Examiner's attention that, while MPEP 2112 provides that inherent disclosures of a prior art reference may be relied upon in the rejection of claims under 35 U.S.C. § 103, MPEP 2141.02 cautions that "[o]bviousness cannot be predicated on what is not known at the time an invention is made, even if the inherency of a certain feature is later established." See MPEP 2141.02(V), citing *In re Rijckaert*, 9F.2d 1531 (USPQ2d 1955 (Fed. Cir. 1993)). MPEP 2141.02(V) identifies only disclosed inherent properties as a part of "as a whole" inquiry into obviousness. Accordingly, even if immunostimulant properties of N-carboxymethyl chitosan, which are not disclosed in Amsden, were later found to be inherent, it would be improper for the Examiner to rely on such later recognized properties when inquiring into obviousness of Claim 52 in view of the combined disclosure of Eyles and Amsden.

The Examiner cites Duncan as providing the disclosure of cationic pluronic, an element of the claims as pending prior to this Response. The claims, as currently amended, do not recite cationic pluronic, and the disclosure in Duncan, on which the Examiner relies in the rejection, is therefore not relevant to the currently amended claims. Applicants assert that the claims, as currently amended, would not have been obvious to one of ordinary skill in the art based on the combined disclosure of Eyles, Amsden and Duncan at least in view of the differences between the claims and the scope of the cited publications, as discussed above. In view of the claim amendments and the foregoing remarks, applicants request withdrawal of the rejection of the claims as obvious over Eyles in view of Amsden and further in view of Duncan.

Amsden in view of Duncan

The Examiner rejects Claims 52, 55-56, 58-63, 66 and 68-71 under 35 U.S.C. §103(a) as obvious over Amsden and in view of Duncan. Applicants cancel Claims 55 and 62, thereby

rendering their rejection moot. Applicants assert that the amendments to independent Claims 52 and 63 overcome the rejection of Claims 52, 56, 58-61, 63, 66 and 58-71. Applicants discussed the scope of Amsden in the previous Responses and also in the preceding section of this Response. In summary, Amsden does not disclose or suggest using N-carboxymethyl chitosan as a separate component of drug-containing microparticles in addition to the microencapsulating polymer, as recited in the pending claims. Besides being one of the many polymers suitable for the production of microparticles, Amsden does not identify or suggest any beneficial properties of N-carboxymethyl chitosan that would make it advantageous for its use in such particles.

Applicants discovered that N-carboxymethyl chitosan acts an immunostimulant, and that including it into microparticles along with an antigen is beneficial to the particles' immunogenic properties. MPEP 2141.02(V) identifies only disclosed inherent properties as a part of "as a whole" inquiry into obviousness. The Examiner failed to identify any disclosure in Amsden suggesting immunostimulant properties of N-carboxymethyl chitosan and failed to provide any reasoning, as required in MPEP 2143.01(IV), as to why one of ordinary skill in the art would include N-carboxymethyl chitosan as an additional component into polymer-microencapsulated drug-containing compositions disclosed in Amsden. Accordingly, the Examiner failed to establish why Amsden would render obvious the claims, as pending prior to the present response.

Duncan is cited by the Examiner as supplying the information about using cationic pluronic block copolymers, which are not recited in the claims as currently amended. Accordingly, the disclosure of Duncan, on which the Examiner relies when making the rejection, is not relevant to the claims, as currently amended. However, applicants note that, on page 10 of the Office Action, the Examiner improperly applied the principles of anticipation by inherent disclosure to the inquiry into obviousness. The Examiner asserts that inherent properties do not need to be recognized by one of ordinary skill of the art at the time of the invention in order to make them relevant to patentability. The Examiner provides several citations to case law in support of her position.

Applicants respectfully assert that the citations provided by the Examiner, all of which are found in MPEP 2112, are relevant to the inquiry of the novelty of the claims. Obviousness

analysis follows a different criterion. MPEP 2141.02 provides that “[o]bviousness cannot be predicated on what is not known at the time an invention is made, even if the inherency of a certain feature is later established.” See MPEP 2141.02(V), citing *In re Rijckaert*, 9F.2d 1531 (USPQ2d 1955 (Fed. Cir. 1993)).” MPEP 2141.02(V) identifies only disclosed inherent properties as a part of “as a whole” inquiry into obviousness. The rule set forth in MPEP 2141.02(V) logically follows from the explanation of an obviousness inquiry provided in MPEP 2142 as an analysis of whether or not the claims were obvious from the point of view of one of ordinary skill in the art at the time of the invention. If a property was not disclosed in the information on which the Examiner relies in her obviousness determination, such an undisclosed property does not affect the obviousness of the claims in view of the cited information from the point of view of one of ordinary skill in the art. Accordingly, applicants assert that, at least under the criteria of MPEP 2141.02(V), Examiner failed to establish why the disclosure of cationic pluronic in Duncan as a stabilizer of squalene emulsions is relevant to the inquiry of the obviousness of the embodiments of applicants’ compositions, in which a cationic pluronic is used as a component of immunogenic microparticles.

The claims, as currently amended, no longer recite a cationic pluronic, an element of the claims pending prior to this Response. The disclosure of Duncan cited by the Examiner in the Office Action is therefore no longer relevant to the pending claims. Applicants assert that, based on the disclosure of Amsden, it would not have been obvious to one of ordinary skill in the art to arrive at compositions in which N-carboxymethyl chitosan is co-encapsulated with a biologically active agent, as recited in Claim 52, or at polymer microspheres surface-modified with N-carboxymethyl chitosan, as recited in Claim 63. Thus, the disclosure of Duncan cited by the Examiner is not relevant to the pending claims, and Amsden fails to render the claims obvious at least in view of the differences between the claims and the scope of the publication. In view of the claim amendments and the foregoing remarks, applicants request withdrawal of the rejection of the claims as obvious over Amsden in view of Duncan.

Amsden and Duncan in view of Cleary et al. (WO 96/21432; “Cleary”)

The Examiner rejects Claims 53-54 under 35 U.S.C. §103(a) as obvious over Amsden and Duncan further in view of Cleary. Applicants cancel Claims 53-54 thereby rendering their

rejection moot. The claim amendments provided in this Response incorporate the limitations of Claims 53-54 into Claim 63, which was not rejected by the Examiner in the relevant section of the Office Action. Applicants therefore request withdrawal of the rejection for at least this reason. Further, applicants respectfully assert that the combination of the publications cited by the Examiner fails to render obvious pending independent Claims 52 and 63, as currently amended, as well as their respective dependent claims.

The scope and content of Amsden, Duncan and Cleary is discussed in the previous Response and elsewhere in current Response. Cleary, in particular, discloses particles comprising an active substance and a mucoadhesive polymer. According to Cleary, the mucoadhesive particles can be produced by uniformly mixing an active substance with a mucoadhesive polymer or by coating the active substance core with a layer of the mucoadhesive polymer. Cleary does not teach or suggest using N-carboxymethyl chitosan as a component of microparticles or as an immunostimulant.

Applicants assert that it would not have been obvious to one of ordinary skill in the art using the combined disclosure of Amsden, Duncan and Cleary to arrive at compositions in which N-carboxymethyl chitosan is co-encapsulated with a biologically active agent, as recited in Claim 52, or at polymer microspheres surface-modified with N-carboxymethyl chitosan and having adsorbed biologically active agent, as recited in Claim 63. All of the cited publications fail to suggest that adding N-carboxymethyl chitosan to the immunogenic polymer microparticles would result in any further improvement of the particles' immunogenic properties.

The Examiner asserts on page 12 of the office Action that Cleary provides the motivation to include a mucoadhesive polymer on the surface of the particles. However, the Examiner fails to substantiate this assertion. Cleary, as well as Amsden or Duncan, fails to disclose or suggest that N-carboxymethyl chitosan can act as a mucoadhesive polymer. The Examiner failed to establish that inherent mucoadhesive properties of N-carboxymethyl chitosan were actually disclosed in Amsden, Cleary or Duncan, and failed to provide any evidence that they were known to one of ordinary skill in the art at the priority date of the present application. MPEP 2141.02(V) provides that only disclosed inherent properties as a part of "as a whole" inquiry into obviousness. Accordingly, even it was later established that N-carboxymethyl

chitosan was inherently mucoadhesive, it is improper to rely on such later recognized property when inquiring into non-obviousness of the pending claims. Applicants therefore assert that a combination of Cleary, Amsden and Duncan fails to render obvious pending claims and request withdrawal of the rejection in view of the claim amendments and the following remarks.

Rejections under 35 U.S.C. 112, second paragraph

The Examiner rejects Claims 52-56, 58-63, 66 and 68-71 under 35 U.S.C. 112, second paragraph, as indefinite, due to the recitation of the term “pluronic.” Applicants assert that the claim amendments deleting the term from the claims rendered the rejection moot. Applicants request withdrawal of the rejection.

CONCLUSION

This Response fully addresses the rejections in the Office Action. Based upon the amendments and remarks provided above, applicants believe that the pending claims are in condition for allowance. A Notice of Allowance is therefore respectfully solicited.

No additional fees are believed due; however, the Commissioner is hereby authorized to charge any additional fees that may be required, or credit any overpayment, to Deposit Account No. 11-0855.

If the Examiner believes any informalities remain in the application that may be corrected by an Examiner's Amendment, or that there are any other issues that can be resolved by a telephone interview, a telephone call to the undersigned attorney at (404) 815-6102 is respectfully solicited.

Respectfully submitted,

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